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ORIGINAL ARTICLE

p-TSA catalysed efficient synthesis of 1,2,4,5-tetraaryl-imidazoles

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Abstract *p*-TSA catalysed simple and efficient synthesis of 1,2,4,5-tetraaryl-imidazoles via a four component condensation of benzoin, aniline, ammonium acetate and araldehydes in ethanol under reflux condition is reported. The yields are high, procedure is mild and less time consuming.

1. Introduction

Naturally occurring substituted imidazoles as well as synthetic derivatives thereof exhibit a wide range of biological activities, making them attractive compounds for biochemists and organic chemists. Imidazoles act as inhibitors of p38 MAP kinase (Lee et al., 1994), B-Raf kinase (Takle et al., 2006), cyclooxygenase-2 (COX-2) (Lange et al., 2005), transforming growth factor b1 (TGF-b1) and type-1 activin receptor-like kinase (ALK5) Khanna et al., 1997 and are useful in the biosynthesis of interleukin-1 (IL-1) Gallagher et al., 1995. Substituted imidazoles are extensively used as glucagon receptors (de Laszlo et al., 1999) and CB1 cannabinoid receptor antagonists (Eyers et al., 1998), modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR) Newman et al., 2000, act as antibacterials (Antolini et al., 1999) and also as antitumor (Wang et al., 2002) agents. Recent advances in *green chemistry* and organometallic catalysis has extended the application of imidazoles as ionic liquids (Dupont et al., 2002) and as N-heterocyclic carbenes (Bourissou et al., 2000; Arnold and Liddle, 2006; Kuhl, 2007). Highly substituted imidazoles are expected to have potential therapeutic activities (Lee et al., 1994).

Methods are available in the literature for the synthesis of imidazoles; to mention a few: 2,4,5-trisubstituted imidazoles are synthesized by a three component cyclocondensation of a 1,2-diketone, or α-hydroxyketone, or an α-ketomonoxime with an aldehyde and ammonium acetate in the presence of catalysts such as ionic liquids (Siddiqui et al., 2005), silica–sulfuric acid (Shaabani and Rahmati, 2006), and $NiCl_2{\cdot}6H_2O/Al_2O_3$ (Heravi et al., 2007). 1,2,4,5-Tetrasubstituted imidazoles, on the other hand, are prepared by a four component reaction of a 1,2-diketone, or an α-hydroxyketone, or α-ketomonoxime with an aldehyde, aniline and ammonium acetate in the presence of catalysts such as $InCl_3{\cdot}3H_2O$ (Das Sharma et al., 2008) and $ZrCl_4$ (Sharma et al., 2006). The developed procedures have both advantages and disadvantages, such as the use of expensive reagents and the environmental hazards associated with their use and prolonged reaction time.

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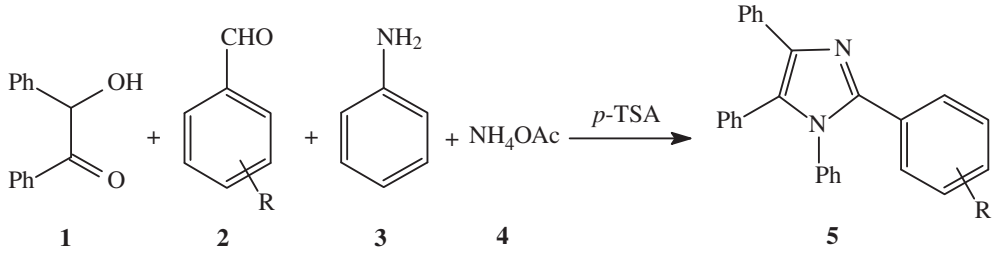
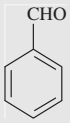
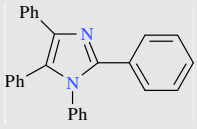
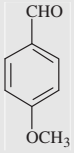
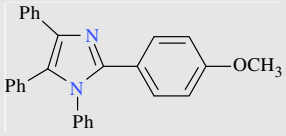
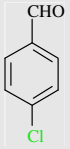
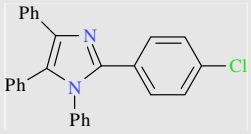
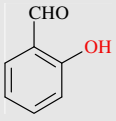
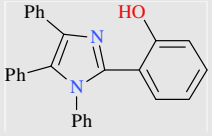
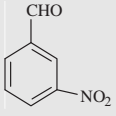
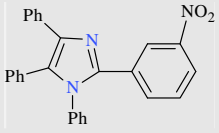
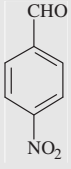
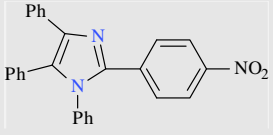
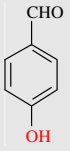
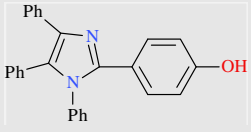
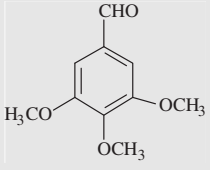
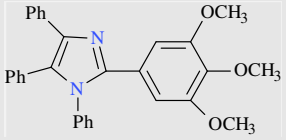
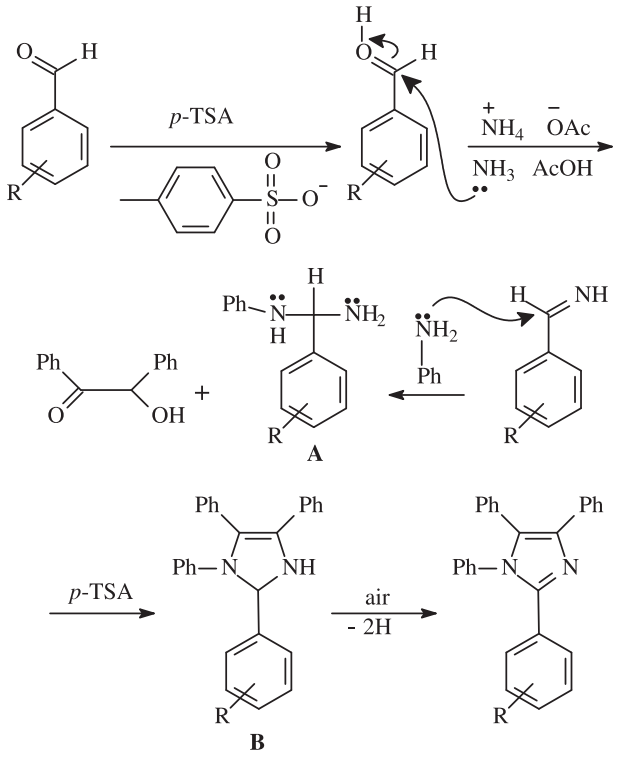


Scheme 1

Table 1 *p*-TSA catalysed synthesis of 1,2,4,5-tetraaryl-imidazoles.

Entry	Aldehyde	Product (**5**)[a]	Reaction time (min)	Yield (%)[b]
a.			30	92
b.			35	90
c.			40	87
d.			40	85
e.			45	80
f.			45	80
g.			40	85
h.			40	89

[a]**5a**, **5e** and **5h** were characterized by ^{1}H NMR and IR spectral analysis. **5b**, **5c**, **5d**, **5f** and **5g** were characterized by comparison on TLC or by their melting points with authentic samples prepared by the reported method (Mazaahir and Poonam, 2006).
[b]Isolated yields.



Scheme 2

As noticed, imidazoles are of enormous biological importance, and we feel that there is a need to synthesize these molecules using simple, readily available and less expensive catalysts in shorter duration of time. We, in our laboratory, have been working on the development of procedures, which can be used to synthesize biologically active molecules using simpler methodologies and readily available catalysts (Pasha and Madhusudana Reddy, 2009; Pasha and Jayashnkara, 2006a,b; Pasha and Nanjundaswamy, 2007). As well known, *p*-TSA (Xiangming and Huiqiang, 2007) has been used as a mild acidic catalyst to synthesize a number of benzimidazoles, and in our laboratory, we have used *p*-TSA to synthesize 1,5-benzodiazepines (Pasha and Jayashnkara, 2006a), bis(indolyl) methanes Pasha and Jayashnkara, 2006b, novel quinolines (Pasha et al., 2008), acylals (Pasha and Manjula, 2007) and nitriles (Pasha et al., 2009). Hence, as an alternative, we planned to use *p*-TSA for the synthesis of 1,2,4,5-tetraaryl-imidazoles from benzoin (**1**), araldehyde (**2**), aniline (**3**) and ammonium acetate (**4**) as shown in Scheme 1.

2. Results and discussion

1,2,4,5-Tetraphenyl imidazole (**5**) was prepared in quantitative yield by condensing benzoin, aniline, and ammonium acetate with benzaldehyde in the presence of *p*-TSA as a catalyst in ethanol as solvent after 30 min. The separated solid was filtered and recrystallized to get the pure product. To optimize the reaction conditions, the reactions were carried out using catalysts such as $Zn(OAc)_2{\cdot}2H_2O$ and $ClSO_3H$; due to unsatisfactory results, these catalysts were rejected. Then, the reaction was carried out using an organo-catalyst *p*-TSA, and positive results were obtained. Encouraged by this, *p*-TSA was used as a model catalyst for further reactions. Optimization of the reaction was done by using different amounts of *p*-TSA [2 mol%, 5 mol% and 10 mol%], and high yield of the product was obtained with 10 mol% of the catalyst. These optimized conditions were applied to get imidazoles from a series of substituted araldehydes and the results of these studies are presented in Table 1. From this table, it is clear that irrespective of the substituents present on the araldehydes the yields of imidazoles did not vary much.

2.1. Mechanism

The reaction can be mechanistically considered to proceed with the protonation of the araldehydes by *p*-TsOH and the subsequent attack by ammonia from ammonium acetate and aniline to give *C*,*N*-diphenyl-methanediamine (**A**), which may react with benzoin in the presence of *p*-TsOH to afford dihydroimidazole (**B**), followed by aerial oxidation (Hoang et al., 2001) to give the product as shown in Scheme 2.

3. Experimental

Yields refer to isolated products after purification. The IR spectra were taken using KBr pellets. IR and ^{1}H NMR spectra were recorded on SHIMADZU FT-IR-8400s and Bruker (300-MHz) spectrophotometers, respectively. The purity of the substances and the progress of the reactions were checked on TLC. The reagents used were all commercial and used without any purification.

3.1. General procedure for the preparation of tetrasubstituted imidazoles

A mixture of benzoin (0.42 g, 5 mmol), aniline (0.47 g, 5 mmol), ammonium acetate (0.38 g, 5 mmol) and araldehyde (5 mmol) was taken in ethanol (10 ml), to which *p*-TSA (0.19 g, 1 mmol) was added. The reaction mixture was then refluxed for 30–60 min. In some cases a solid separated which was filtered and in cases where solid did not separate, cold water (10 ml) was added to get the solid. The crude products were then subjected to further purification either by recrystallization from EtOH or by silica gel column chromatography.

*3.2. Spectral studies of 2-(3-nitrophenyl)-1,4,5-triphenyl-imidazole (**5e**)*

The formation of yellow solid 2-(3-nitrophenyl)-1,4,5-triphenyl-imidazole was confirmed by the melting point [245–246 °C (Lit. m.p. 244–246 °C)]. IR spectrum showed characteristic peaks at 1598 cm^{-1} for C=C and at 1575 cm^{-1} for C=N. The ^{1}H NMR spectrum supported the structure of 2-(3-nitrophenyl)-1,4,5-triphenyl-imidazole showing a multiplet between δ 7.10–8.96 ppm for aromatic protons.

4. Conclusion

In conclusion, we report a simple, mild and efficient method for the preparation of the 1,2,4,5-tetraarylimidazoles. The reagents used here are readily available, less expensive and easy to handle. The procedure reported herein is not cumbersome; consequently, the methodology represents a good addition to the list of methods available for the synthesis of highly substituted imidazoles.

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